BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellant(s): Blue, Jeffrey T.

Application Number: 10/030,378

Filing Date: November 9, 2001

Title of the Invention: DETECTION OF VIRAL STABILITY

Examiner: Le, Emily M.

Art Unit: 1648

APPEAL BRIEF

37 C.F.R. 1.8 Certificate of Mailing

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MERCK & CO., INC.

By Sheldon Heber Date 9-21-06

Sheldon Heber

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REAL PARTY IN INTEREST

The real party in interest is Merck & Co., Inc.

RELATED APPEALS AND INTERFERENCES

There are no pending related appeals and interferences. An appeal brief was filed for the present application on May 4, 2005. Subsequent to the May 4, 2005 appeal brief, the patent office provided new rejections and reopened prosecution. The May 4, 2005 appeal did not go before the Board of Patent Appeals and Interferences.

STATUS OF CLAIMS

Claims 1-8 and 18-25 are pending and stand rejected. The rejections to all the pending claims are appealed.

STATUS OF AMENDMENTS

A final amendment was filed May 22, 2006 addressing objections to claims 20 and 21. The advisory action mailed June 14, 2006 indicated that for purposes of appeal the amendment would be entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The present application describes using viral induced caspase 3 activity to provide a measure of viral activity. (The present application at page 1, lines 23-24.) The application notes that assaying viral induction of caspase 3 activity is useful, for example, in methods measuring viral potency and stability and for evaluating the stability of a virus in different formulations. (The present application at page 1, lines 24-26.)

Measuring viral induced caspase 3 activity provides an alternative assay to using a plaque forming unit (PFU) assay to measure viral activity. The PFU assay is a prior art assay that measures viral activity based on the ability of a virus to infect cells and cause plaque formation, or areas on dead or detached cell. (The present application at page 1, lines 11-20.)

Independent claim 1 is directed to a method measuring viral induced caspase 3 activity as an indication of viral activity to obtain an indication of virus stability and potency from either: (i) a virus present in two different formulations or (ii) a virus in the same formulations at two different time points. The method involves (a) contacting cell susceptible to caspase 3 induction with a virus from a first formulation and (b) measuring caspase 3 activity as an indication of virus activity. Steps (a) and (b) are repeated using either the virus taken from (i) a different formulation or (ii) from the same formulation at a different time. (The present application at page 1, lines 22-31 and page 5, lines 18-19.)

Independent claim 18 is directed to a method for assaying activity of measles virus, mumps virus, or rubella virus, by measuring viral induced caspase 3 activity. The method involves contacting cells susceptible to caspase 3 induction with the virus and measuring caspase 3 activity as an indication of virus activity. (The present application at page 1, lines 22-31 and page 3, lines 13-15.)

The present application provides different examples illustrating the use of viral induced caspase 3 activity to provide a measure of viral activity and illustrating different embodiments. The provided examples include experiments describing a correlation between viral induced caspase 3 activity and virus activity, the reproducibility and linearity of the caspase 3 assay, and using the caspase 3 assay to measure viral activity, viral potency, and viral stability in samples under different conditions.

A correlation between viral activity and caspase 3 signal is illustrated in the present application using different viral dilutions and by comparing results obtained with the caspase 3

assay to results obtain with a PFU assay. The effect of different viral dilutions is summarized in Tables 5 and 6. (The present application on page 11, line 5 to page 12, line 2.) As the multiplicity of infection decreased through viral dilution, caspase 3 signal correspondingly decreased. Figures 4-6 provide results comparing the caspase 3 assay to a PFU assay.

The reproducibility of the caspase 3 assay is illustrated in the present application by repeating the assay using three vials of the same sample. (The present application at page 10, line 19 to page 11, line 4, including Table 4.)

The linearity of the caspase 3 assay is illustrated by measuring caspase 3 activity at different time following viral induction. (The present application at page 9, lines 1-10 and Figures 2a and 2b.) Figure 2a illustrates that the assay is linear for at least one hour using measles virus. Figure 2b illustrates that the assay is linear for at least 75 minutes using mumps virus.

Figure 3 provides viral activity for different samples in RFU (reflective fluorescent units). (The present application at page 2, lines 22-26 and page 12, lines 4-13.) The RFU for a particular sample provided a direct measure of viral potency. The RFU from different samples provided a measure of viral stability under the different conditions.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Claims 1-8 and 18-25 stand rejected under 35 U.S.C. § 112, Second Paragraph, as allegedly lacking an essential steps

II. Claims 1-3 and 7 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953)

III. Claims 4, 5, 18 and 19 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Duncan *et al.* (Virology 255, 117-128, 1999)

IV. Claim 6 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Wu *et al.* (provisional application 60/108606, priority document to U.S. Patent No. 6,689,600)

V. Claim 8 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Goodrich *et al.* (U.S. Patent No. 5,958,670)

VI. Claim 22 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Esolen *et al.* (Journal of Virology, June 1995, p. 3955-3958)

VII. Claims 1, 20, 23 and 25 stand rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Wu *et al.* (provisional application 60/108606, priority document to U.S. Patent No. 6,689,600)

ARGUMENT

I. Claims 1-8 and 18-25 Comply with 35 U.S.C. § 112, Second Paragraph

Claims 1-8 and 18-25 stand rejected as allegedly lacking an essential step. The examiner argues the claims: (1) fail to recite a nexus between the difference in caspase 3 activity and the determination of viral stability and potency; (2) fail to provide a particular incubation time; and (3) fail to set forth a standard or fixed evaluation condition. (Office Action mailed February 22, 2006, paragraph number 4, pages 2-3.) The examiner indicates the rejection is based on 35 U.S.C. § 112, second paragraph, and the Manual of Patent Examining Procedure (MPEP) § 2172.01. (Office Action mailed February 22, 2006, at page 2, fourth paragraph.)

The rejection appears to be directed to the absence of particular parameters in the claims concerning different conditions such as incubation time. (Advisory action mailed June 14, 2006, at page 2, sixth paragraph.)

The rejection fails to consider the nature of the invention, the level of skill in art, and the teachings provided in the application. The present invention involves measuring viral induction of caspase 3 as an indication of viral activity. Independent claims 1 and 18 both functionally indicate measuring caspase activity as an indication of virus activity. The particular conditions employed for such measuring can vary and were within the level of skill in the art at the time the application was filed.

MPEP § 2172.01, cited by the examiner to support the rejection, is directed to a claim that omits matter disclosed in the application to be "essential" to the invention. The provided rejection fails to indicate where the present application describes a particular parameter as "essential" to the invention. The Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

The application itself broadly refers to the invention as measuring viral induction of caspase 3 activity to provide a measure of viral activity. (See, for example the present application in the Summary of the Invention on page 1, lines 22-26 and the Abstract.) The MPEP § 2164, at page 2100-206, points out the relevance of broad language in describing the invention and ensuring that the limitation is described as "critical".

> Therefore, an enablement rejection based on the grounds that a disclosed critical limitation is missing from a claim should be made only when the language of the specification makes it clear that the limitation is critical for the invention to function as intended. Broad language in the disclosure, including the abstract, omitting an allegedly critical feature, tends to rebut the argument of criticality.

MPEP § 2164, Rev. 5, August 2006, at page 2100-206, first column, lines 1-8.

Different assay conditions are illustrated in the examples provided in the application. (The present application at page 5, line 21 to page 12 line 22.) The application expressly notes that such examples are for illustration purposes and are not limiting to the claimed invention:

> Examples are provided below to further illustrate different features and advantages of the present invention. The examples also illustrate useful methodology for practicing the invention. These examples do not limit the claimed invention.

(The present application at page 5, lines 22-24.)

(1) Nexus Between Caspase 3 Activity Differences and Viral Stability and Potency

The examiner asks whether viral stability and potency is present, absent, significant, insignificant, substantial or insubstantial when caspase 3 activity is more or less in one formation compared to another. (Office Action mailed February 22, 2006, page 2, last paragraph.)

Claim 1 refers to measuring caspase 3 activity as an indication of viral activity in a formulation or different formulations. The difference in caspase 3 activity for a virus taken from a first and second formulation is indicated in claim 1 to provide an indication of virus stability and potency in the first formulation compared to the second formulation. The difference in caspase 3 activity for a virus taken from a first formulation at two or more time intervals is indicated in claim 1 to provide an indication of virus stability and potency in the first formulation.

The rejection goes to how the results of the assay are interpreted and not to an essential step for performing the assay itself. As indicated in the claims, the difference in activity provides an indication as to viral stability and potency. The present invention is not based on how magnitudes of difference in activity are evaluated by the skilled artisan. Such an evaluation was readily within the ability of one of ordinary skill in the art when the application was filed.

(2) Incubation time

The examiner argues that the present application at page 9, lines 9-10 promotes the use of a 1-hour incubation period for caspase 3 activity. (Office Action mailed February 22, 2006, page 3, first paragraph.) While a 1-hour incubation time is preferred, the application does not refer to a particular incubation time, such as 1-hour, as a "critical" part of the invention.

Assays in general can be performed taking measurements at different incubation time points. Preferably, a time point is taken when the activity is linear with time. The present application provides data illustrating that a particular incubation time is not critical even for obtaining a time point when the activity is linear with time. In the same paragraph noted by the examiner, the application mentions that for measles virus the assay is linear for "at least" one hour, and for mumps virus the assay is linear for "at least" 75 minutes. (The present application at page 9, lines 1-10.) The indicated minimum times of one hour and 75 minutes each provides a broad time range indicating a particular time is not critical.

(3) Standard or Fixed Evaluation Conditions

The examiner argues that the claims lack reference to a standard or fixed evaluation condition and such a limitation is necessary for a meaningful analysis. (Office Action mailed February 22, 2006, page 3, second paragraph.) The examiner fails to indicate where the application references a standard or fixed evaluation conditions as an essential part of the invention.

Standard or fixed evaluation conditions might be preferred for performing an assay. However, the application does not describe particular conditions as critical for the invention. For example, the skilled artisan can perform the assays under different conditions where there is some variability in the assay results and still obtain meaningful information. Adjusting conditions for performing an assay, and the effect of changing a particular condition, was well within the ability of the skilled artisan when the application was filed.

II. Claims 1-3 and 7 are not anticipated under 35 U.S.C. § 102(b) by Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953)

Claims 1-3 and 7 stand rejected as allegedly anticipated by Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953). The rejection is directed to

step (ii) where the virus is taken from the first formulation at two or more time intervals. The examiner argues Banki *et al.* teaches the active steps of (a) contacting cells susceptible to caspase 3 induction with a virus, wherein the virus induced caspase 3 activity, and (b) measuring said caspase 3 activity, wherein steps (a) and (b) are repeated at two or more time intervals. The examiner refers to Banki *et al.* at page 11946, Figure 2, with caption; page 11948, 1st sentence, last full paragraph; and page 11949, Figure 5 with caption. (Office Action mailed February 22, 2006, paragraph number 8, pages 5-7.)

The Banki *et al.* sections noted by the examiner fail to repeat both steps (a) and (b), as provided for in Claim 1 Step (ii). Step (a) indicates contacting cells with the virus from a first formulation. Step (b) indicates measuring caspase 3 activity. Step (ii) describes repeating both the contacting step and the measuring step.

Banki *et al.* describes a continuous time-course for measuring HIV induced apoptosis. Banki *et al.* initially infects a set of cells, then at different times measures apoptosis from the initially infected cells. Banki *et al.*, does not appear to repeat the cell infection step using HIV obtained from a first formulation at different times.

Anticipation requires each and every element as set form in the claim to be described expressly or inherently in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), *cert. denied,* 484 U.S. 827 (1987).

The examiner argues that Banki *et al.* repeated both steps (a) and (b) with the virus taken from a first formulation at two or more time interval. (Advisory action mailed June 14, 2006, at page 2, seventh paragraph.) However, the examiner fails to specifically point to where Banki *et al.* describes repeating each of the steps of taking a virus from a first formulation, infecting cells, and measuring caspase 3 activity at different times. The Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d at 1445, 24 USPQ2d at 1444.

III. Claims 4, 5, 18 and 19 are not obvious under 35 U.S.C. § 103(a) based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Duncan *et al.* (Virology 255, 117-128, 1999)

Claims 4, 5, 18 and 19 stand rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* in view of Duncan *et al.* (Virology 255, 117-128, 1999). Duncan *et al.* is cited for teaching Vero and RK13 cells are susceptible to caspase 3 activity and that rubella induces caspase 3 activity. The examiner argues that Duncan *et al.* is deficient in not teaching measurement of caspase 3 activity and that one skilled in the art would be motivated to combine Banki *et al.* with Duncan *et al.* to quantify viral induced apoptosis. (Office Action mailed February 22, 2006, paragraph number 10, pages 7-9.)

Obviousness under 35 U.S.C. § 103 is examined in light of the following four factual inquires: (1) the scope and content of the prior art; (2) the differences between the prior art and claims at issue; (3) the level of ordinary skill in the art; and (4) secondary considerations. *Graham v. John Deere*, 148 USPQ 459, 467 (U.S. Sup.Ct. 1966).

To establish a *prima facie* case of obviousness based on a combination of references the patent office must show some objective teaching in the prior art, or that knowledge generally available to one of ordinary skill in the art, that would lead one of ordinary skill in the art to combine the relevant teachings of the references. *In Re Fine,* 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). A prior art reference must be considered in its entirely including portions teaching way from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock Inc.,* 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir 1983), *cert. denied,* 469 U.S. 851 (1984).

For this rejection, the claims are grouped as follows: (A) claims 4 and 5; and (B) claims 18 and 19. Claims 4 and 5 ultimately depend on claim 1. Claim 18 is a separate independent claim. Claim 19 depends from claim 1.

A. Claims 4 and 5

Claims 4 and 5 by virtue of their dependency from claim 1, include the claim 1 description concerning repeating steps (a) and (b). As noted above in Argument II *supra.,* Banki *et al.* fails to describe such steps. Duncan *et al.* is not cited for curing the deficiencies in Banki *et al.*

Claims 4 and 5 further distinguish Banki *et al.* in view of Duncan *et al.* based on the description concerning the virus being either measles, mumps or rubella. Duncan *et al.* teaches measuring apoptosis in general by quantifying detached cells. The proposal to modify Duncan *et al.* to measure caspase 3 activity as indication of viral activity is inconsistent with Duncan *et al.* looking for effects caused by apoptosis in general.

Duncan *et al.* is not concerned with measuring viral activity. Duncan *et al.* concerns studying the cellular basis of the ability of the rubella virus to cause system birth defects in the fetuses of infected women. (See Duncan *et al.* abstract, first two sentences.) Duncan *et al.* indicates that other caspases, in addition to caspase 3, are involved the observed apoptosis. (Duncan *et al.*, at page 125, first column, third paragraph.)

Banki *et al.* measures caspase 3 activity to study HIV induced apoptosis. Banki *et al.* fails to provide motivation to modify Duncan *et al.* to specifically look at caspase 3 activity alone or in combination with other particular caspases, as an indication of viral activity.

B. Claims 18 and 19

Claims 18 and 19 are directed to a method for assaying activity of measles, mumps or rubella by measuring the ability of the virus to induce caspase 3 activity. Duncan *et al.* teaches measuring apoptosis in general by quantifying detached cells. The examiner's proposal to modify Duncan *et al.* to measure caspase 3 activity as indication of viral activity is inconsistent with Duncan *et al.* looking for effects caused by apoptosis in general.

Duncan *et al.*, is not concerned with measuring viral activity. Duncan *et al.* concerns studying the cellular basis of the ability of the rubella virus to cause system birth defects in the fetuses of infected women. (See Duncan et al. abstract, first two sentences.) Duncan *et al.* indicates that other caspases, in addition to caspase 3, are involved the observed apoptosis. (Duncan *et al.*, at page 125, first column, third paragraph.)

Banki *et al.* measures caspase 3 activity to study HIV induced apoptosis. Banki *et al.* fails to provide motivation to modify Duncan *et al.* to specifically look at caspase 3 activity alone or in combination with other particular caspases, as an indication of viral activity.

IV. Claim 6 is not obvious 35 U.S.C. § 103(a) based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Wu *et al.* (provisional application 60/108606, priority document to U.S. Patent No. 6,689,600)

Claim 6 stands rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* as applied to claims 1-3 in view of Wu *et al.* (provisional application 60/108606, priority document to U.S. Patent No. 6,689,600). Wu *et al.* is cited for teaching that lyophilization improves stability of viral vaccine and recombinant proteins. (Office Action mailed February 22, 2006, paragraph number 11, page 9.)

Claim 6 depends from claim 1. As noted in Argument II *supra.*, claim 1 distinguishes Banki *et al.*, for example, by indicating steps (a) and (b) are repeated at two or more time intervals. Wu *et al.* fails to cure such deficiencies in Banki *et al.*

V. Claim 8 is not obvious under 35 U.S.C. § 103(a) based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Goodrich *et al.* (U.S. Patent No. 5,958,670)

Claim 8 stands rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* as applied to claims 1-3 in view of Goodrich *et al.* (U.S. Patent No. 5,958,670). Goodrich *et al.* is cited for teaching a method of storing cells by freezing and later thawing. (Office Action mailed February 22, 2006, paragraph number 12, pages 9-10.)

Claim 8 depends from claim 1. As noted in Argument II *supra.*, claim 1 distinguishes Banki *et al.*, for example, by indicating steps (a) and (b) are repeated at two or more time intervals. Goodrich *et al.* fails to cure such deficiencies in Banki *et al.*

VI. Claim 22 is not obvious under 35 U.S.C. § 103(a) based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Esolen *et al.* (Journal of Virology, June 1995, p. 3955-3958)

Claim 22 further describes the virus of claim 18 as either measles or mumps. Claim 22 stands rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* in view of Esolen *et al.* (Journal of Virology, June 1995, p. 3955-3958). Banki et al is cited for teaching a method of measuring caspase 3 activity to quantify virally induced apoptosis. Esolen *et al.* is cited for teaching that measles virus induces apoptosis. The examiner argues it would be *prima*

facie obvious to combine Banki *et al.* with Esolen *et al.* to quantify apoptosis induced by measles virus. (Office Action mailed February 22, 2006, paragraph number 13, pages 10-11.)

Esolen *et al.* is not concerned with determining viral activity. Esolen *et al.* is directed to determining the mechanism of measles virus-induced cell death. (See Esolen *et al.* abstract on page 3955.) Esolen *et al.* notes that DNA fragmentation indicative of apoptosis was apparent by flow cytometry, agarose gel electrophoresis and election microscopy. (See Esolen *et al.* abstract on page 3955.)

The skilled artisan would not be motivated to modify Esolen *et al.* using the methods employed by Banki *et al.* to determine the mechanism of measles virus-induced cell death. Esolen *et al.* does not reference caspase 3 activity as involved in the observed cell death or indicate that caspase activity should be quantified. Banki *et al.* measures caspase 3 activity to study HIV induced apoptosis.

VII. Claims 1, 20, 23 and 25 are not obvious under 35 U.S.C. § 103(a) based on Banki *et al.* (The Journal of Biological Chemistry May, 8, 1998; Vol 273, No. 19, 11944-11953) in view of Wu *et al.* (provisional application 60/108606, priority document to U.S. Patent No. 6,689,600)

Claims 1, 20, 23 and 25 stand rejected as allegedly obvious under 35 U.S.C. § 103(a) based on Banki *et al.* as applied to claim 18 in view of Wu *et al.* The rejection is directed to reference in the claims to measurement of caspase 3 activity from two different formulations. Banki *et al.* is cited for teaching a method of measuring caspase 3 activity to quantify viral induced apoptosis. Wu *et al.* is cited for teaching the significance of formulations on biological activity. The examiner argues that one of ordinary skill in the art would be motivated to determine the effect of the formulation on the biological activity and structural integrity of the virus. (Office Action mailed February 22, 2006, paragraph number 14, pages 11-12.)

For this rejection, the claims are grouped as follows: (A) claims 1 and 25; and (B) claim 20; and (C) claim 23. Claim 25 ultimately depends on claim 1. Claims 20 and 23 ultimately depend from claim 18.

A. Claims 1 and 25

The rejection fails to indicate particular modifications to Banki *et al.* or Wu *et al.* Instead the rejection generally alleges the two references should be combined to provide an assay to determine the effects of a formulation on viral activity. The Patent Office bears the initial burden of presenting a *prima facie* case of unpatentability. *In re Oetiker* 977 F.2d at 1445, 24 USPQ2d at 1444.

The fact that formulations can affect viral activity, does not provide motivation to measure caspase 3 activity as an indication of viral activity in different formulations. Banki *et al.* concerns studying HIV induced apoptosis. Banki *et al.* does not indicate that caspase 3 activity should be measured to provide an indication of viral activity in comparing formulations. Wu *et al.* teachings on the significance of formulations on biological activity fail to cure such deficiencies.

B. Claim 20

As noted in Argument VII.A *supra.*, the rejection fails to indicate particular modifications to Banki *et al.* or Wu *et al.* Instead the rejection generally alleges the two references should be combined to provide an assay to determine the effects of a formulation on viral activity. Claim 20 further distinguishes the cited references by indicating the virus is either measles, mumps or rubella.

C. Claim 23

As noted in Argument VII.A *supra.*, the rejection fails to indicate particular modifications to Banki *et al.* or Wu *et al.* Instead the rejection generally alleges that the two references should be combined to provide an assay to determine the effects of a formulation on viral activity. Claim 23 further distinguishes the cited references by indicating the virus is either mumps or rubella.

CONCLUSION

Appellants request that the Board of Patent Appeals and Interferences reverse the outstanding rejections of claims 1-8 and 18-25.

Please charge deposit account 13-2755 for fees due in connection with this Appeal Brief. If any time extensions are needed for the timely filing of the present Appeal Brief, Appellants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

By 

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CLAIMS APPENDIX

1. A method for assaying activity of a virus to determine viral stability and potency comprising the steps of:

(a) contacting a plurality of cells susceptible to caspase 3 induction with said virus obtained from a first formulation, wherein said virus induces caspase 3 activity; and

(b) measuring said caspase 3 activity as an indication of virus activity,

wherein said steps (a) and (b) are repeated with either: (i) said virus taken from a second formulation, said second formulation being different than said first formulation, and the difference in caspase 3 activity from said virus taken from said first and second formulation provides an indication of virus stability and potency in said first formulation compared to said second formulation; or (ii) said virus taken from said first formulation at two or more time intervals and the difference in caspase 3 activity between said two or more time intervals provides an indication of virus stability and potency in said first formulation.

2. The method of claim 1, wherein said caspase 3 activity is measured using a caspase 3 substrate linked to a fluorimetric or a colorimetric moiety.

3. The method of claim 2, wherein said substrate is the peptide Asp-Glu-Val-Asp (SEQ ID NO: 1).

4. The method of claim 3, wherein said virus is either measles virus, mumps virus, or rubella virus.

5. The method of claim 4, wherein said plurality of cells is either Vero cells or RK-13 cells.

6. The method of claim 3, wherein prior to said step (a) said virus was lyophilized.

7. The method of claim 1, wherein said steps (a) and (b) are repeated with said virus taken from said first formulation at two or more time intervals.

8. The method of claim 3, wherein after said step (a) and prior to said step (b) said cells were frozen and then thawed.

18. A method for assaying activity of a virus comprising the steps of:

(a) contacting a plurality of cells susceptible to caspase 3 induction with said virus, wherein said virus is either measles virus, mumps virus, or rubella virus; and

(b) measuring said caspase 3 activity as an indication of virus activity.

19. The method of claim 18, wherein said plurality of cells is either Vero cells or RK-13 cells.

20. The method of claim 18, wherein said steps (a) and (b) is performed to determine the caspase 3 activity of said virus present in a first formulation and in a second formulation, said second formulation being different than said first formulation, wherein the difference in caspase

3 activity in said first and second formulation provides an indication of virus stability and potency in said first formulation compared to said second formulation.

21. The method of claim 18, wherein said method is performed to determine the caspase 3 activity of said virus present in a formulation at two or more time intervals, wherein said virus is removed from said formulation at two or more time intervals and the activity is measured by performing said step (a) followed by said step (b) at said two or more time intervals, wherein the difference in caspase 3 activity at said two or more time intervals provides an indication of virus stability and potency in said formulation.

22. The method of claim 18, wherein said virus is either measles virus or mumps virus.

23. The method of claim 20, wherein said virus is either measles virus or mumps virus.

24. The method of claim 21, wherein said virus is either measles virus or mumps virus.

25. The method of claim 1, wherein said steps (a) and (b) are repeated with said virus taken from a second formulation different from said first formulation.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Blue, Jeffrey T.		Art Unit: 1648
Serial No.:	10/030,378	Case No.: 20455P	
Filed:	November 9, 2001		Examiner: Le, Emily M.
For:	DETECTION OF VIRAL STABILITY		

Commission for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FEE AUTHORIZATION

Sir:

Please charge deposit account 13-2755 $160 for fees believed due in connection with the filing of a brief in support of an appeal. Applicant previously paid $340 for filing a brief in support of an appeal for the above-referenced application on May 4, 2005. Subsequent to filing the May 4, 2005 appeal brief, the case was reopened by the patent office and did not go before the Board of Patent Appeals and Interferences. The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account 13-2755. Duplicate copies of this sheet are enclosed.

Respectfully submitted,

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By _____ Date September 21, 2006

Sheldon O. Heber